REMARKS

Introduction & Support for Amendments

Before entry of the foregoing amendment, claims 1-5, 7-27, 37 and 38 were pending and examined on the merits. Upon entry of the foregoing amendment, claim 7 will be canceled, claims 39-41 will be added and claims 1, 4, 8-12 and 37-38 will be amended. Accordingly, claims 1-5, 8-27 and 37-41 are now pending, of which claims 1, 37, 39 and 40 are in independent form.

The claim amendments and newly added claims are supported by the specification as originally filed.[1] In particular, support in claim 1 and for the phrase, "a first variable domain" can be found, e.g., at page 8, line 3. Support in claims 1 and 37 for the phrase, "corresponding inter-domain interface" is found, for example, at page 4, lines 3-6, in conjunction with page 5, lines 26-31. Support in claims 1, 37, 39 and 40 for the phrase, "wherein said first variable domain is capable of interacting with a second variable domain to form a functional antibody molecule or fragment thereof" can be found, for instance, at page 8, lines 14-19. Support for the phrase, "wherein said variable heavy domain is capable of interacting with said variable light domain to form a functional scFv" in claim 37 can be found, e.g., at page 7, lines 25-28; and page 19, line 32 through page 20, line 3. Support for the term "comprising" in claim 4 can be found e.g., at page 7, lines 2-3. The amendments to claims 8-12 are clerical in nature and/or make changes in light of terminology modified in a base claim from which they depend. Support in

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[1] Page and line references refer to the clean version of the Substitute Specification submitted on August 29, 2002.

claims 39 and 40 for "former interface" can be found, inter alia, at page 4, lines 8-12 of the Specification.

Prior Art Rejections over Johnson

There are only two related issues that remain in this case: (i) a novelty rejection over Johnson et al. (WO 92/01787) ("Johnson") and (ii) an obviousness rejection under 35 U.S.C. § 103(a) that relies upon Johnson as the primary reference. Specifically, claims 1-5, 7-11, 13-17, 26-27 and 37-38 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Johnson, while claims 1-5, 7, 10-11, 13-27 and 37-38 are rejected as obvious under 35 U.S.C. 103(a) over Johnson in view of Jenkins et al. (PNAS 92:6057-6061, 1995) and Knappik et al. (Biotechniques 17(4):754-761, 1994) and Dubel et al. (J. Immunol. Met. 178:201-209, 1995) and Kostelny et al. (J. Immunol. 148:1547-1533, 1992).

The claimed invention and Johnson both teach certain formats of immunoglobulins having modified domains. The heart of the rejections over Johnson continues to implicate the perceived overlap in subject matter between the modifications taught by Johnson and the modifications called for by the independent claims of the instant invention.

1. Prior Proceedings

Thus far, Applicants have pointed out that Johnson narrowly focuses on enhancing the yield of functional single domain antibodies (i.e., a variable heavy or a variable light),

conventionally referred to as an "Fv fragment." At the time of <u>Johnson</u>, it had been well-known in the art that single domain antibodies suffer from poor or inefficient folding, as well as high levels of non-specific binding that "disappointingly limit their utility" (<u>Johnson</u> at page 2, line 5). <u>Johnson</u>, thus, attempted to overcome these drawbacks by (i) identifying the amino acid residues that form the hydrophobic region in the Fv fragment and (ii) mutating those residues to less hydrophobic amino acids (<u>see</u> <u>Johson</u> at pages 6-7). More specifically, <u>Johnson</u> teaches modifying amino acids of an Fv fragment at the region where the Fv fragment would otherwise associate with its variable domain complimentary domain (<u>i.e.</u>, a variable heavy domain is the compliment of a variable light domain and vice-versa) (<u>Johnson</u> at page 13, lines 19-22).

With regard to Applicants' invention, Applicants have pointed out that the modifications called for by the instant claims are distinct from the modifications taught by <u>Johnson</u>. For instance, Applicants have stated that the then-pending claims were directed to modifications of the "inter domain" interface, rather than in the interface where a heavy chain variable domain and a light chain variable domain typically associate.[2]

2. <u>Basis for Maintained Rejections</u>

Despite Applicants' arguments, the extant Office Action maintains the prior art rejections, stating:

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[2] The instant Specification at page 4, lines 1-7 refers to an "inter-domain" interface as the interface that would exist between a V_H/C_{H1} or a V_L/C_H.

while the examiner acknowledges the distinctness of the two types of interfaces, by reciting the phrase "inter-domain interface," the instant claims do not exclude an inter-domain interface between the heavy and light chain variable regions in certain recombinant antibody molecules such [as] single chain antibodies.

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...the examiner notes that Johnson teaches on page 15 alterations to frameworks that enable the generation of antibodies as well as single chain variable domains with improved properties....

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Johnson further teaches on page 13 that antibodies include the immunoglobulin isotypes and Fab, scFv, Fv, dAb and Fd fragments. Therefore Johnson reads on said new claims.

(Paper No. 33 at page 2, penultimate paragraph and paragraph bridging pages 2-3).

Accordingly, the foundation underlying the Examiner's position is that Johnson teaches

functional antibody formats that contain a first variable domain capable of interacting

with a second variable domain, e.g., scFv and Fab.

3.   **Clarifying the Scope of Johnson**

Applicants respectfully re-submit, however, that the Examiner's interpretation of

Johnson is overbroad and that Johnson, when properly construed, does not adversely

affect the patentability of any pending claim from either a novelty or obviousness point-

of-view. In other words, Johnson does not teach any functional antibody formats that

contain a first variable domain capable of interacting with a second variable domain to

form a functional antibody molecule or functional fragment thereof (e.g., scFv or Fab).

8

a. Johnson only teaches modifying single variable domains

It is paramount to recognize that page 15 of Johnson only teaches the generation of altered "single variable domains eg. VH domains..." (emphasis added). The Examiner appears to equate the terms "single variable domain" and "single chain variable domain" as used in Johnson with the conventionally understood "single chain variable fragment" (scFv); however, similarity in nomenclature does not, in this instance, equate to similarity in structure. Throughout the disclosure of Johnson, it is apparent that a "single variable domain" and "single chain variable domain" refer to a V_H or V_L domain (see e.g., p. 3, ll. 3-7; p. 3, l. 15; p. 3., l. 21; p. 4, l. 23; p. 4, ll. 27-28; p. 5, l. 14; p. 9, ll. 3-4; p. 14, ll. 12-14; p. 18, ll. 3-13; and p. 31, l. 8 of Johnson). A scFv, on the other hand, requires a V_H domain and V_L domain having a linker interspaced therebetween. Accordingly, Applicants respectfully urge that the Examiner has misinterpreted page 15 of Johnson, inasmuch as Examiner interprets Johnson as teaching modified scFv's or any other antibody format requiring the interaction of two variable domains.

b. Johnson's definition of an "antibody" must not be read out of context

Applicants agree with the Examiner that Johnson states at page 13: "Example antibodies are the immunoglobulin isotypes and the Fab, $F(ab')_2$, scFv, Fv, dAb, Fd fragments." Applicants respectfully disagree, however, that this excerpt is evidence that Johnson teaches an antibody variable domain modified such that it is able to interact with a second variable domain to form a functional antibody molecule or fragment thereof.

First, it is important not to read out-of-context this excerpt from Johnson, which is contained within the "Terminology" section of the application, beginning at the bottom of

page 11. This section of Johnson proceeds to define terms such as "binding domain," "immunoglobulin," "antibody" and "immunoglobulin superfamily" according to conventionally recognized definitions. It is, therefore, not surprising for Johnson to include the undisputed statement that "Example antibodies" are the immunoglobulin isotypes and the Fab, F(ab^{1})$_2$, scFv, Fv, dAb, Fd fragments. What Johnson does not say, however, is which of those antibody formats are contemplated by his invention. That Johnson does not contemplate using two-variable domain antibody formats (e.g., Fab and scFv) is underscored by the observation that Johnson repetitively speaks of "single variable domain" Fv domains (i.e., unpaired V_H and V_L domains), yet not once mentions a Fab or scFv format outside of this passage to refer to his invention.

      c.   Johnson's "background" section disclaims "paired" antibody fragments

The "background" section of Johnson buttresses this point. There, Johnson refers to various problems associated with single variable domains:

> VH domains have unique disadvantages that disappointingly limit their utility... They are expressed in low quantities when cloned in bacteria... and during purification of VH domains, substantial amounts of material are lost... This probably reflects non-specific binding to surfaces.

(Johnson at page 2, lines 4-15). Johnson proceeds to identify antibodies formats that are not riddled with the same problems as unpaired Fv fragments:

> These difficulties are not generally experienced with whole antibodies or with fragments of antibodies such as Fv or Fab fragments. Therefore, the problems appear to be a characteristic of antibody fragments containing unpaired single domains.

(Id. at page 2, lines 22-26) (emphasis added). Johnson then associates his invention with those antibody formats that suffer from the above-identified drawbacks:

> Thus, the present invention seeks to ameliorate any of the above or other problems associated with single variable domain binding members.

Thus, this "Background" section unequivocally limits Johnson's invention to antibody fragments containing unpaired single domains.

d. Objective evidence clarifies the contours of Johnson

Second, and despite how the above page 13 excerpt is interpreted, Johnson does not enable the production of a modified antibody fragment containing a variable domain that is capable of interacting with a second variable domain to form a functional antibody molecule or fragment thereof. As persuasive, objective evidence to support their position, Applicants refer to the Rule 132 Declaration executed by Prof. Dr. Andreas Plückthun, a co-inventor in the present application (the "Plückthun Declaration"). The Examiner is urged to consider the factual statements within the Plückthun Declaration as objective evidence, which carry more weight than arguments alone. See MPEP § 716(c) (August, 2001), while bearing in mind that it is improper to disregard the statements contained in the Plückthun Declaration simply because Dr. Plückthun is a named inventor in this case. See Ex parte Keyes, 214USPQ 579 (Bd. App. 1982); MPEP, Id. Should the Examiner disagree with any portion of the Plückthun Declaration, Applicants request the Examiner to support the basis for any disagreement with objective evidence.

With reference to paragraph nine of the Plückthun Declaration, <u>Johnson</u> teaches modifying amino acid residues in "the region on a given heavy or light chain of an immunoglobulin which associates with the complementary heavy or light chain" (<u>Johnson</u> at page 13, lines 19-22). <u>Johnson</u> made these modifications in order "to ameliorate... problems associated with single variable domain binding members" (page 2, line 27 through page 3, line 1), namely "problems... characteristic of antibody fragments containing <u>unpaired</u> single domains" (page 2, lines 23-26) (emphasis added).

<u>Johnson</u> specifically describes mutating residues H37, H39, H45, H47, H91, H93 and H103 in the variable heavy domain of a single variable domain binding member, since these residues <u>normally interact</u> with the VL counterpart domain (<u>see</u> page 23, lines 4-7) (emphasis added). These residues play a role in the interaction between an antibody variable domain and its variable domain counterpart.

Thus, as stated at paragraph eight of the Plückthun Declaration, one of ordinary skill in the art would expect that making one or more of the variable domain modifications taught by <u>Johnson</u> would prevent the interaction between the modified antibody variable domain and its variable domain counterpart. In other words, it would be impossible to construct a two-variable domain antibody format (<u>e.g.</u>, Fab or $F(ab^1)_2$) using a variable domain modified in accordance with the teachings of <u>Johnson,</u> since these formats require, by definition, the interaction between a variable heavy and a variable light domain. Further, the formation of a functional scFv antibody format would be impossible following <u>Johnson's</u> teachings, since this antibody format requires that the

two variable domains, which are expressed within a single polypeptide chain, must interact with each other.

4. The Anticipation Rejections Should be Withdrawn

In sum, for the reasons described above, Johnson neither teaches nor enables the construction of any functional antibody formats that contain a first variable domain capable of interacting with a second variable domain to form a functional antibody molecule or functional fragment thereof, which is required by each pending claim. Accordingly, Johnson fails to describe each and every element of the claimed invention, and withdrawal of the rejection is respectfully solicited. See Verdegaal Bros. v. Union Oil Co. of Calif., 814 F.2d 628, 631 (Fed. Cir. 1987); see also MPEP § 2121 (referring to the requirement that prior art must contain an "enabling disclosure").

5. The Obviousness Rejections Should be Withdrawn

For the reasons described above, Johnson fails to teach or suggest functional antibody formats that contain a first variable domain capable of interacting with a second variable domain to form a functional antibody molecule or functional fragment thereof. Instead, Johnson narrowly suggests the modification of amino acids at the portion of a "single variable domain" that otherwise would interact with its variable domain compliment, and Johnson specifically sanctions the making of these modifications in order to inhibit this interaction. Johnson, in effect, teaches away from Applicants' claimed invention. See In re Grasselli, 713 F.2d 731, 743 (Fed. Cir. 1983).

13

None of the relied-upon secondary references make up for the deficiencies of Johnson, or would have suggested to one of ordinary skill in the art that modifying the teachings of Johnson would somehow lead to the claimed invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 103(a).

Conclusion:

In view of the foregoing, Applicants respectfully request the Examiner to withdraw each rejection and pass the claims to allowance. The Examiner is invited to contact the undersigned attorney to resolve any issues, in order to expedite the prosecution of the application.

Respectfully submitted,

5:19.03
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Marked Up Copy of Claims

1.   (~~Five~~ Six times amended) A DNA sequence encoding ~~a domain of a functional~~ an antibody molecule or functional fragment thereof, comprising (i) a first variable domain, and (ii) a modification of an inter-domain interface as compared to a corresponding ~~domain or fragment~~ inter-domain interface of a parent antibody molecule or fragment thereof, wherein said modification results in said ~~domain or fragment of said antibody~~ antibody molecule or functional fragment thereof demonstrating increased hydrophilicity as compared to said ~~domain or fragment of said~~ parent antibody- molecule ~~in unmodified form,~~ and wherein said first variable domain is capable of interacting with a second variable domain to form a functional antibody molecule or fragment thereof.

4.   (~~Three~~ Four times amended) The DNA sequence according to claim 1 in which said modification ~~consists of~~ comprises any two or more of:

   a)   a substitution of one or more amino acids at said region which comprised or would comprise the interface with amino acids which are more hydrophilic than the one or more amino acids being substituted for;

   b)   an insertion of one or more hydrophilic amino acids or insertion of amino acids; and

   c)   a deletion of one or more hydrophobic amino acids or deletion of amino acids.

7.   (Canceled) ~~(Amended) The DNA sequence according to claim 1 in which said domain or fragment is derived from an antibody.~~

8.   (Twice Amended) The DNA sequence according to claim 1, wherein ~~in which~~ said DNA sequence encodes a functional antibody fragment, and wherein said fragment is a Fab fragment.

9.   (Twice Amended) The DNA sequence according to claim 1, wherein ~~in which~~ said DNA sequence encodes a functional antibody fragment, and wherein said fragment is an Fv fragment.

10.   (Twice Amended) The DNA sequence according to claim 1, wherein ~~in which~~ said DNA sequence encodes a functional antibody fragment, and wherein said fragment is a scFv fragment.

11.   (Twice Amended) The DNA sequence according to claim ~~1~~ 9, wherein ~~in which~~ said Fv fragment is ~~an Fv~~ stabilized by an inter-domain disulphide bond.

12.   (~~Twice~~ Thrice Amended) The DNA sequence according to ~~any of claims~~ claim 9 ~~to~~ or 11, wherein ~~in which~~ said variable domain is a variable light domain (VL) or a variable heavy domain (VH), and wherein said inter-domain interface comprises residues 9, 10, 12, 15, 39, 40, 41, 80, 81, 83, 103, 105, 106, 106A, 107, 108 for VL, and residues 9, 10, 11, 13, 14, 41, 42, 43, 84, 87, 89, 105, 108, 110, 112, 113 for VH.

37.   (Amended) A DNA sequence encoding ~~a domain of a functional antibody or~~ a functional antibody fragment ~~thereof~~, comprising (i) a variable heavy domain, (ii) a variable light domain, and (iii) a modification of an inter-domain interface in said variable heavy or said variable light domain, as compared to a ~~domain or fragment~~ corresponding inter-domain interface of a parent antibody molecule or functional fragment thereof, wherein said modification results in said ~~domain or fragment of said antibody~~ functional antibody fragment demonstrating increased hydrophilicity as compared to said ~~domain or fragment~~ parent antibody molecule, ~~of said parent antibody~~

16

~~in unmodified form~~and wherein said variable heavy domain is capable of interacting with said variable light domain to form a functional scFv.

38.   (Amended) A DNA sequence according to claim 37, comprising (i) a modification of an inter-domain interface in said variable heavy domain, as compared to a ~~domain or fragment~~ corresponding inter-domain interface of a parent antibody; and (ii) a modification of an inter-domain interface in said variable light domain, as compared to a ~~domain or fragment~~ corresponding inter-domain interface of a parent antibody.